

### ***Remarks***

Upon entry of the foregoing amendment, claims 41-65 and 67 to 69 are pending in the application, with claims 1 and 67 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Office reconsider all outstanding objections and rejections and that they be withdrawn.

#### ***I. Withdrawn Rejections and Objections***

Applicants thank the Examiner for the withdrawal of all previous rejections and objections.

#### ***II. Rejections under 35 U.S.C. § 103(a)***

##### ***A. The Claimed Invention Would Not have Been Obvious over the Combination of Bussemakers, Clements and Goessl***

The rejection of claims 41-50, 57, 58, 61, 63, 65, 67 and 68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bussemakers *et al.* USPN 7,008,765 ("Bussemakers") in view of Clements *et al.*, *The Journal of Urology* 161:1337-1343 (1999) ("Clements") and Goessl *et al.*, *Cancer Research* 60:5941-5945 (2000) ("Goessl") is respectfully traversed.

Claim 1 of the invention recites, *inter alia*, a method for determining a predisposition for developing prostate cancer or a presence of prostate cancer in a patient comprising performing an RNA amplification assay on a urine sample of the patient, wherein the sample comprises at least one prostate cell or nucleic acid extract thereof and the urine sample does not comprise semen.

As discussed in more detail below, the claims would not have been obvious over the cited references. Indeed, the claimed invention could not have been predicted in light of the teachings of the cited references. Further, there would not have been a rationale for combining the teachings of the cited references to arrive at the present invention. In fact, the cited references actually *teach away* from the methods of the invention.

As the Office has noted at page 5 of the Office Action, “Bussemakers does not specifically teach methods using a urine sample, a urine sample not containing semen or a urine sample obtained after digital rectal examination” of the patient for determining a predisposition for developing prostate cancer or a presence of prostate cancer in a patient comprising performing an RNA amplification assay on such a sample. It is respectfully asserted that the Office erroneously states that the deficiencies of Bussemakers are made up in the teachings of Clements and Goessl.

Clements does not cure the deficiencies of Bussemakers. The purpose of Clements is “[t]o determine whether prostatic cells were normally present in *ejaculate*” [Clements Abstract (emphasis added)]. In contrast to the present invention, Clements studied both ejaculate and urethral washings (containing semen) for the presence of *prostate cells*, not PCA3 mRNA, or any prostate cancer specific marker whatsoever. Clements, page 1338: Urethral washings are “small volumes (up to 50 ml.) of voided urine immediately after ejaculation.” [*Id.*]. Therefore, both the ejaculate and the urethral washings contain semen (i.e., spermatozoa and secretions from accessory glands such as prostatic fluid). In contrast, the claims of the present invention recite assaying a urine sample from a patient, wherein the urine sample *does not comprise semen*. Thus, Clements is completely silent on the detection of (a) *a prostate cancer specific marker*,

and particularly PCA3 mRNA; and (b) a prostate cell or a prostate marker in urine *not containing semen*. Indeed, Clements, at page 1341, left column teaches “...that these markers [PSA, PSM and Apolipoprotein D] ***are not cancer specific*** and/or that there may [be] other cells expressing these genes that are derived from a non-prostatic source” (our emphasis). Therefore, neither Clements nor Bussemakers teach or suggest, *inter alia*, assaying urine that does not contain semen for PCA3 mRNA.

Thus, neither Bussemakers nor Clements, alone or combined, teach that the detection of an elevated level of the prostate cancer-specific PCA3 mRNA sequence in urine not containing semen, as compared to a level thereof associated with a normal or non-malignant prostate state, is indicative of a higher risk of developing prostate cancer or a presence of prostate cancer in the patient. Likewise, neither reference teaches or suggests, alone or combined, an absence of detection of the prostate cancer-specific PCA3 mRNA sequence or lower level thereof in urine not containing semen, as compared to a level thereof associated with a normal or non-malignant prostate state, is indicative of an absence of prostate cancer or a lower risk of developing same, when a prostate-specific mRNA is detected, thereby validating the presence of at least one prostate cell or RNA extract thereof.

Goessl does not cure the deficiencies of Bussemakers or Clements. Indeed, as discussed in more detail below, Goessl actually teaches away from the recited methods. Goessl reports using fluorescent methylation-specific PCR of *DNA-based* detection of prostate cancer in bodily fluids. In contrast to the claimed invention, Goessl is completely silent on performing an *RNA amplification assay* using the recited prostate

cancer-specific PCA3. PCA3 mRNA can be unstable and degraded easily and neither Bussemakers, Clements nor Goessl indicate that such a marker can be found in urine.

Further, Goessl tests the following tissues/bodily fluids in its method for DNA-based detection of prostate cancer: (a) prostate tumors; (b) white blood cells, (c) serum or plasma, (d) ejaculate and (e) urine after 1 minute of digital prostate massage [i.e., Goessl, page 5941]. Obtaining urine after digital prostate massage is *not recited* in claim 41 of the invention. In contrast, Goessl *requires* that urine be collected after prostate massage. Thus, Goessl does not teach performing an *RNA* amplification assay on urine that does not comprise semen. In direct contrast, Goessl teaches performing a *DNA based test on urine samples*.

In addition, Goessl teaches away from the present invention. The results of the study in Goessl would have given one of skill in the art no confidence in using a urine-based test for the determination of the presence of prostate cancer. As noted, Goessl performs a DNA based assay using a prostate cancer marker, GSTP1 promoter hypermethylation. Goessl found that "94% of prostate cancer tissues (16 of 17) exhibited GSTP1 promoter hypermethylation as well as 72% of plasma or serum samples (23 of 32), 50% of ejaculate (4 of 8), and **36% of urine samples after prostatic massage** (4 of 11; Fig. 3 and Table 1)" [Goessl, page 5942 (emphasis added)]. Goessl thus teaches that their worst results are obtained with urine collected immediately after prostate massage: *only 36%* of patients with prostate cancer tested positive for the presence of this prostate marker. In contrast, 94% of prostate cancer tumors exhibited the presence of this prostate cancer marker (and 50% of ejaculate). Goessl thus *teaches away* from a method for determining a predisposition for developing prostate cancer or a

presence of prostate cancer in a patient comprising assaying a urine sample from a patient that does not comprise semen. The small percentage of urine samples that tested positive in Goessl would not give one of skill in the art confidence regarding using a urine-based test for the detection of prostate cancer or for the determination of a predisposition for developing prostate cancer.

The success of the claimed invention therefore was not predictable from the cited prior art. A common theme throughout the obviousness rationales cited in the MPEP is that the results of combining the cited art must be *predictable* in order for the invention to be found obvious. MPEP, Section 2143, 8<sup>th</sup> Edition, August 2007. The Supreme Court in *KSR International v. Teleflex Inc.*, 550 U.S. 398 (2007) identified a number of rationales to support a conclusion of obviousness and the MPEP describes several exemplary rationales [*Id.*, page 2143]. For example, rationale "A" in the MPEP is based on combining prior art elements according to known methods to yield predictable results [*Id.*]. Under this rationale, to conclude that a claim would have been obvious, the Office must show that:

all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and ***the combination yielded nothing more than predictable results to one of ordinary skill in the art.***

[*Id.* (emphasis added)]. As demonstrated above, the claimed elements of the invention are not present in the cited art. Further, one of skill in the art would not have combined the cited art to yield "nothing more than predictable results." In fact, one of skill in the art would have been *discouraged* from using a urine-based test for determining a predisposition for developing prostate cancer or a presence of prostate cancer based on

the cited art. Goessl in particular illustrates that a urine-based prostate cancer test (*even after prostate massage to release semen*) would not be accurate in determining the presence of prostate cancer. The results of combining the cited references were therefore by no means predictable.

For at least the above reasons, it is respectfully requested that the Office withdraw the rejection under 35 U.S.C. § 103.

***B. The Claimed Invention Would Not have Been Obvious over the Combination of Bussemakers, Clements, Goessl and Cheung***

The rejection of claims 41-50, 57, 58, 61-65, 67 and 68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bussemakers in view of Clements and Goessl and further in view of Cheung, *J. Clin. Microbiol.* 10:2593-2597 (1994) ("Cheung") is respectfully traversed.

The combination of Bussemakers, Clements and Goessl do not teach or suggest the claimed invention. Cheung does not cure the deficiencies of Bussemakers, Clements and Goessl. Cheung describes a method for detecting hepatitis C virus RNA by using silica particles. Cheung is silent regarding a method for determining a predisposition for developing prostate cancer or a presence of prostate cancer in a patient comprising assaying a urine sample from that patient, wherein the urine sample comprises no semen.

The Office cites Cheung as teaching a method of extracting RNA from a sample using a silica-based method. However, Cheung differs from the claimed invention in several respects. Cheung describes extracting hepatitis C virus RNA by using silica particles [Cheung, page 2593]. In contrast, the claims of the invention recite extracting a prostate cancer-specific PCA3 mRNA, not a viral RNA. Further, Cheung describes

extracting viral RNA in *serum* [*Id*]. By contrast, the claims of the invention recite extracting prostate cancer-specific PCA3 mRNA in *urine* [*Id*].

Accordingly, Cheung does not cure the deficiencies of Bussemakers, Clements and Goessl. Withdrawal of the rejection is therefore respectfully requested.

***C. The Claimed Invention Would Not have Been Obvious over the Combination of Bussemakers, Clements, Goessl and Baret***

The rejection of claims 41-50, 57-61, 63, 65 and 67-69 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bussemakers in view of Clements and Goessl and further in view of Baret, EP 0 256 932 ("Baret") is respectfully traversed.

The combination of Bussemakers, Clements and Goessl do not teach or suggest the claimed invention. Baret does not cure the deficiencies of Bussemakers, Clements and Goessl. Baret describes the use of oxidase enzyme systems in chemiluminescent assays. Baret is silent regarding a method for determining a predisposition for developing prostate cancer or a presence of prostate cancer in a patient comprising assaying a urine sample from that patient, wherein the urine sample comprises no semen.

Accordingly, Baret does not cure the deficiencies of Bussemakers, Clements and Goessl. Withdrawal of the rejection is therefore respectfully requested.

***D. The Claimed Invention Would Not have Been Obvious over the Combination of Bussemakers, Clements, Goessl and Buck***

The rejection of claims 41-51, 54, 57, 58, 61, 63, 65, 67 and 68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bussemakers in view of Clements and Goessl and further in view of Buck, *Biotechniques* 27(3):528-536 (1999) ("Buck") is respectfully traversed.

The combination of Bussemakers, Clements and Goessl do not teach or suggest the claimed invention. Buck does not cure the deficiencies of Bussemakers, Clements and Goessl. Buck describes a survey of strategies of sequencing primer selection and evaluated primer performance in automated DNA sequencing [Buck, page 528]. Buck is silent regarding a method for determining a predisposition for developing prostate cancer or a presence of prostate cancer in a patient comprising assaying a urine sample from that patient, wherein the urine sample comprises no semen.

The Office alleges that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in using a primer pair comprising SEQ ID NOs:3 and 4 to detect PCA3 and a primer pair comprising SEQ ID NOs: 1 and 2 to detect PSA [OA, page 14]. The Office further recites Buck for the proposition that basically any set of primer sequences throughout a known nucleotide will work to amplify the sequence [OA, page 13]. However, Buck teaches that "under optimal sequencing conditions with *highly pure template and primer*, many of the commonly applied primer design parameters are dispensable" [Buck, page 528 (emphasis added)]. The present invention describes performing an RNA amplification assay on a *urine sample not containing semen*. For example, the specification of the present invention states that "[i]n another embodiment, the methods of the present invention are carried out using a crude, unpurified, or semi-purified sample" [Specification, paragraph [0027]]. *Under such conditions, the template is not "highly purified" and the teachings of Buck are immaterial.*

Accordingly, none of the cited references teach or even suggest the use of the primer pairs recited in claims 51 and 54. Further, one of skill in the art would not have



had a reasonable expectation of success of using these particular primers. The teachings of Buck do not give such a reasonable expectation of success under the assay conditions of the present invention.

Accordingly, Buck does not cure the deficiencies of Bussemakers, Clements and Goessl. Withdrawal of the rejection is therefore respectfully requested.

***E. The Claimed Invention Would Not have Been Obvious over the Combination of Bussemakers, Clements, Goessl and Schlegel***

The rejection of claims 41-50, 52, 53, 55-58, 61, 63, 65, 67 and 68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bussemakers in view of Clements and Goessl and further in view of Schlegel, US 2002/0168638 ("Schlegel") is respectfully traversed.

The combination of Bussemakers, Clements and Goessl do not teach or suggest the claimed invention. Schlegel does not cure the deficiencies of Bussemakers, Clements and Goessl. Schlegel describes compositions, kits and methods for detecting, preventing, and treating prostate cancer. Schlegel is silent regarding a method for determining a predisposition for developing prostate cancer or a presence of prostate cancer in a patient comprising assaying a urine sample from that patient, wherein the urine sample comprises no semen.

Accordingly, Schlegel does not cure the deficiencies of Bussemakers, Clements and Goessl. Withdrawal of the rejection is therefore respectfully requested.

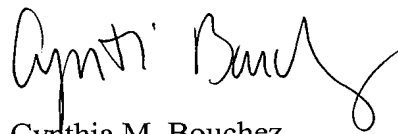
***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Cynthia M. Bouchez  
Attorney for Applicant  
Registration No. 47,438

Date: January 30, 2009

1100 New York Avenue, N.W.  
Washington, D.C. 20005-3934  
(202) 371-2600